Congressional Update: Report from the Biomedical Imaging Program of the National Cancer Institute

Molecular Imaging in Cancer:

Future Directions and Goals of the National Cancer Institute¹

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Cancer continues to be a major health problem throughout the world. Imaging of the patient with cancer continues to be an important and integral aspect of radiology practice and patient care. Newer, noninvasive imaging methods have made it possible to better assess and diagnose both primary and metastatic lesions. Prior to the development of these newer imaging technologies and procedures, the patient had few options for diagnosis and staging of suspected malignancy other than exploratory surgery or limited radiologic evaluations. Over the past 2 decades, however, technical advancements, refinements, and development of noninvasive imaging procedures have substantially improved the quality of medical care, and the care of the patient with cancer in particular.

During the past decade we have been fortunate to witness a revolution in our basic understanding of all human disease, including cancer. This has been made possible by the rapid development of basic molecular biologic techniques and methods. These advancements have allowed scientists to identify and determine the DNA sequence of important disease-causing human genes, elucidate important molecular pathways, automate DNA sequencing, determine protein-specific causes of disease, use cultured cell lines to rapidly test drugs and therapies, and develop transgenic animal models. Associated with these developments in basic molecular biology, the imaging sciences have made remarkable advances in technologies and methods.

Acad Radiol 2000; 7:905-907

Molecular, functional, and metabolic imaging techniques currently allow the imaging clinician or scientist to visualize important disease-causing physiologic, cellular, and molecular processes in living tissue. These newly developed techniques allow visualization and quantitation of clinically relevant physiologic variables such as blood flow, oxygen consumption, glucose metabolism, proliferative activity, and tissue hypoxia as they take place in living cells and tissues. As basic scientists gain a better understanding of the fundamental molecular nature of cancer, molecular, cellular, and metabolic imaging techniques will be an important adjunct in translating this knowledge into clinical practice. Molecular imaging can potentially identify altered gene products, molecular pathways, and tumor-specific receptors. This important information may further elucidate how the tumor behaves and will respond to certain drugs, treatments, and therapies.

Further development of targeted contrast agents, ligands, and imaging probes will allow for the in vivo elucidation of those important and key metabolic pathways and specific cell cycle functions that become altered in cancer. With continued evolution of molecular imaging techniques and technology, it will be possible to visualize and quantitate intracellularly the critical changes as the cell transforms from normal to precancerous to cancerous. It will potentially be possible to evaluate at-risk patients earlier in cancer pathogenesis, perhaps before a tumor has even had the chance to become malignant. It is anticipated that with the information obtained from the use of molecular imaging techniques, the actual molecular signatures of cancer will be visualized in vivo. The molecular imaging specialist will be able to visualize and determine which genes are being expressed in a specific cancer and be able to translate this information directly into better clinical care of the patient. In other words, the ability to detect—through

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noninvasive, in vivo molecular and cellular imaging—the molecular changes associated with a tumor cell will vastly improve our ability to detect and stage tumors, select appropriate treatments, monitor the effectiveness of a treatment, and determine prognosis.

These developments will occur across all of the conventional disciplines of imaging including computed tomography (CT), ultrasound (US), magnetic resonance (MR) imaging, and nuclear medicine. Newer techniques such as optical imaging hold particular promise for the detection and elucidation of disease pathogenesis at the microscopic level, potentially even in situ.

To facilitate the development of molecular imaging technologies, there will be associated developments in image enhancement agents, imaging probes, and imaging ligands. These developments will improve our ability to capture changes in the biochemical composition of cells and other living structures. Imaging agents, including contrast agents, probes, and ligands, can contribute to improved image formation in any of three ways: (a) they can localize in certain body organs or structures (anatomic localization), (b) they can attach to specific molecules in the body (receptor localization), or (c) they can become activated by certain biochemical or physical conditions, such as the presence of a specific enzyme or low oxygen concentration in the cell (activatable agents). It is anticipated that contrast agents, imaging probes, and ligands of the future will also be able to reveal the functional and molecular characteristics of tumors that determine clinical behavior and response to therapy.

In imaging, as elsewhere in cancer research, animal models of cancer are making it possible to perform certain kinds of studies that are difficult, if not impossible, to perform in humans. In addition to learning more about cancer, research with animal models will facilitate imaging technology improvements and developments that then may eventually be applied to the clinical care of patients with cancer. A distinct advantage of noninvasive imaging in animal models of cancer is the ability to perform repetitive, noninvasive observations of the biologic processes underlying cancer growth and development without sacrificing the animal. Furthermore, the level of resolution with some small animal imaging modalities is now approaching the size of individual cells. Imaging in animals can also help assess the effectiveness of new instruments and therapeutic technologies such as radiation therapy and directed drug therapies.

MOLECULAR IMAGING IN CANCER: THE GOALS

Over the past several years, the National Cancer Institute (NCI) has been keenly aware of the potential power of imaging techniques and molecular imaging in particular. The Biomedical Imaging Program (http://cancer.gov/bip/default.htm) of the Division of Cancer Treatment and Diagnosis is responsible for the extramural grant portfolio and programs related

to oncologic imaging. Imaging has been identified as an area of "Extraordinary Opportunity" in the past several NCI Bypass Budgets (http://2001.cancer.gov/imaging.htm). The NCI Bypass Budget (http://2001.cancer.gov/2001.htm) is a public document produced annually by NCI to identify for the Administration and Congress those scientific priorities on which the budget appropriation will be spent. The imaging-related goals of the NCI include the following: (a) to develop and validate imaging technologies and agents (eg, probes, radiocontrast agents) that have the sensitivity to detect precancerous abnormalities or very small cancers, (b) to develop imaging techniques that identify the biologic properties of precancerous of cancerous cells that will predict clinical course and response to interventions, (c) to develop minimally invasive imaging technologies that can be used in interventions and in assessing treatment outcomes, (d) to foster interaction and collaboration among imaging scientists and basic biologists, chemists, and physicists to help advance imaging research, and (e) to create infrastructures to advance research in developing, assessing, and validating new imaging tools, techniques, and assessment methods.

The NCI has already made substantial progress in the past several years toward reaching these goals with the introduction of various programs and initiatives:

- 1. NCI has awarded three grants to support In-Vivo Cellular and Molecular Imaging Centers (ICMIC) (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-99-004.html). The ICMIC grants will facilitate interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging because the integration of this breadth of expertise is still in its early stages.
- 2. The NCI has also funded nine pre-ICMIC planning grants (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA -99-002.html). The pre-ICMIC planning grants provide time and funds for investigators and institutions to prepare themselves, organizationally and scientifically, to establish an ICMIC.
- 3. Small animal models, particularly genetically engineered mice, are powerful discovery tools, but we have yet to capitalize fully on their potential in cancer research. NCI has funded five Small Animal Imaging Resource Programs (SAIRP) (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-98-023.html). This initiative supports activities to develop and apply a wide variety of imaging modalities that focus on functional, quantitative imaging. Quantification of image data for small animals will lead the way to quantitative methods that can be applied in humans. An additional five SAIRPs will be funded in fiscal year 2001.
- 4. New drug discovery programs are producing an increasing number of molecules for investigation, in turn stimulating a need for research that integrates imaging techniques into preclinical and clinical studies to assess newly developed therapeutic agents. NCI has set aside funding for the development and application of labeled therapeutic agents as compounds for imaging studies and imaging agents that serve as

metabolic markers of response to newly developed therapeutic agents. The Development of Clinical Imaging Drugs and Enhancers (DCIDE) (http://cancer.gov/bip/dcide.htm) program will facilitate the development of novel imaging agents in preclinical development. A detailed overview of the newly approved DCIDE program will be presented at a future date in Academic Radiology.

MOLECULAR IMAGING IN CANCER: MEETING THE GOALS

To ensure that the initially defined goals for molecular imaging are met and completed in future years, the NCI has set forth in the 2001 Bypass Budget specific priorities and initiatives. These include the following:

- 1. Accelerate development of clinically useful technologies for detecting malignant and precancerous cells and for visualizing their functional characteristics.
- a) Expand the number of ICMICs. This will be accomplished by re-issuing the Request for Applications for the ICMIC Planning grants (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-01-010.html) and re-issuing the Request for Applications for the Molecular and Cellular Imaging Centers (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-01-014.html) again in 2001, 2003, and 2004.
- b) Expand the (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-01-012.html) SAIRP to improve access to researchers testing new approaches to diagnosis, treatment, and prevention in animal models of cancer. NCI will foster collaborations between this program and the Mouse Models of Human Cancers Consortium (MMHCC).
- c) Support multidisciplinary centers of expertise to develop optical technologies and perform clinical feasibility tests of instruments able to visualize epithelial tissue at risk for common cancers and recognize the optical signatures of precancerous abnormalities. This often involves molecule-oriented techniques.
- 2. Develop, synthesize, validate, and distribute to the research community novel imaging agents.
- a) Expand a program similar to NCI's Rapid Access to Intervention Development (RAID) initiative (which is designed to accelerate the movement of novel intervention from the laboratory to the clinic) specifically for imaging agent development. The DCIDE program (http://cancer.gov/bip/dcide.htm) will facilitate and promote preclinical development and validation of important imaging agents and ligands. NCI will, on

- a competitive basis, synthesize, test, and distribute probes that image the physiologic and functional status of tumor tissue in the human body. The DCIDE program will be described in detail in a future issue of *Academic Radiology*.
- b) Establish a publicly available database of agents available to the research community, together with information on their properties.
- 3. Expand and improve clinical studies of molecule-based imaging modalities and image-guided interventions.
- 4. Integrate molecular and functional imaging technologies into drug development and early clinical trials (http://cancer.gov/bip/concepts.htm c4).
- *a*) Support the development of in vivo and molecular clinical imaging research tools for assessing the biologic effect of cancer drugs on their intended target or pathway.
- b) With this continued investment in the future of imaging research, it will soon be possible to apply the techniques developed to image novel molecular targets, specific genetic pathways, signal transduction, cell cycle alterations, angiogenesis, apoptosis, and numerous other biologically relevant processes known to occur in cancer in routine clinical practice.

MOLECULAR IMAGING IN CANCER: THE STATE OF THE ART

This document is intended to provide an overview of the NCI's goals for molecular imaging of cancer in the future. With the continued support of the NCI and the intellectual capabilities and determination and hard work of investigators throughout the world currently involved in molecular imaging research, it is likely that the NCI goals and visions of molecular imaging in cancer research and patient care will be met. It is gratifying to note that the power of molecular imaging with positron emission tomography, nuclear medicine techniques, MR spectroscopy, US, CT, optical imaging, and numerous other techniques is being recognized and these techniques are becoming available in routine clinical practice. These modalities will allow for the molecular, functional, biochemical, and physiologic assessment of important aspects of malignancy. Many of these imaging techniques are already beginning to show their potential power in the care of the patient with cancer. With the continued advancements that we hope will occur, imaging will assume a critical and essential role in the basic scientific understanding, diagnosis, staging, and monitoring of cancer.